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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/163,272	09/29/98	DINSMORE J	DNI-041

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AMY E. MANDRAGOURAS
LAHIVE AND COCKFIELD
28 STATE STRTEET
BOSTON MA 02109

EXAMINER	
KERR, J	
ART UNIT	PAPER NUMBER
1633	11

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/163,272	Applicant(s) Jonathan Dinsmore
	Examiner Janet M. Kerr	Group Art Unit 1633

☒ Responsive to communication(s) filed on *Jun 12, 2000* .

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-8, 10-26, and 28-44* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-8, 10-26, and 28-44* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

— SEE OFFICE ACTION ON THE FOLLOWING PAGES —

Response to Amendment

Applicants' amendment, filed 6/12/00, has been entered.

Claims 9 and 27 have been canceled.

Claims 39-44 have been added.

Claims 1-8, 10-26, and 28-44 are pending.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 18-26, 28-37, 43 and 44 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating a xenogeneic subject having spinal cord damage as observed in the hemi-sected animal model or having spinal cord damage as observed in the animal model of amyotrophic lateral sclerosis, does not reasonably provide enablement for a method of treating a xenogeneic subject having spinal cord damage resulting from the claim-designated neurodegenerative disorders per se, the claim-designated spinal cord injuries per se, or aging. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Applicant's arguments with respect to the claims have been considered but are moot in view of the new ground(s) of rejection.

While the specification is enabling for a method of treating a xenogeneic subject having spinal cord damage as observed in the hemi-sected animal model or having spinal cord damage as observed in the animal model of amyotrophic lateral sclerosis by administering porcine spinal cord cells to areas of the injured spinal cord, the specification is non-enabling for methods of treating any neurodegenerative disorder such as degeneration of cells in the spinal cord, physical deterioration, death of spinal cord cells, abnormal pattern of spinal cord cells, amyotrophic lateral sclerosis, multiple sclerosis, syringomyelia, spinal tumors or metastasis, and spinal cord infections, or aging. The specification discloses a particular model system for spinal cord lesions, i.e., a hemi-sected animal model, wherein pig spinal cord cells are transplanted into the region of the lesion, and a model system for amyotrophic lateral sclerosis. The specification, however, does not disclose a particular method of treating all of the claim-designated neurodegenerative diseases, spinal cord injuries or aging, per se, such that therapeutic effectiveness is achieved in mammals suffering from degeneration of cells in the spinal cord, physical deterioration, death of spinal cord cells, abnormal pattern of spinal cord cells, multiple sclerosis, syringomyelia, spinal tumors or metastasis, and spinal cord infections, or aging. There is no nexus between the animal models disclosed in the instant application and the claim-designated conditions. In addition, the specification does not disclose where the spinal cord cells should be administered, whether the spinal cord cells are a heterogeneous or homogeneous population of cells, the amount of spinal cord cells to be administered, or the age of the cells to be administered, i.e., the time during embryonic development in which the cells were isolated. Moreover, the prior art does not describe suitable animal models which can be used to determine the therapeutic efficacy of transplanting porcine spinal cord cells to treat the claimed conditions. Thus, absent adequate guidance in the specification and absent teachings in the prior art of suitable animal model systems to use in the claimed methods, it would require undue experimentation for the skilled artisan to practice the invention as claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 8, 10-12, 25, 36, 37, and 42-44 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 8 and 25 are rendered vague and indefinite by the phrase "capable of" as it is unclear under what conditions the antigen on the cell surface has the capability of stimulating an immune response against the cell.

Claim 10 is rendered vague and indefinite by the phrase "into the human" as there is no human recited in claim 8. The phrase lacks antecedent basis.

Claim 36 is rendered vague and indefinite by the phrase "wherein spinal cord damage is spinal cord injury" as it is unclear what the distinction is between "damage" and "injury". Clarification is requested.

Claim 37 is rendered vague and indefinite by the phrase "wherein the spinal cord damage is a neurodegenerative disorder" as it is unclear how a damaged spinal cord can be a neurodegenerative disorder. Clarification is requested.

Claim 40 is rendered vague and indefinite for the following reasons: it is unclear what the distinction is between "spinal cord damage" and "spinal cord injury"; it is unclear how a damaged spinal cord can be a neurodegenerative disorder; and it is unclear how a damaged spinal cord can be aging.

Claims 42 and 44 are rendered vague and indefinite by the inclusion of "spinal cord injury" in the elements of the Markush group directed to neurodegenerative disorder as spinal cord injury appears to be a distinct Markush group in claim 40. It is unclear how "spinal cord injury" can be considered one distinct group and yet be a Markush element in a different group. Clarification is requested. Claims 42 and 44 are also rendered vague and indefinite by the phrases "physical deterioration" and "abnormal pattern of spinal cord cells" as it is unclear what is deteriorating and

what type of pattern of spinal cord cells is considered abnormal. Claims 42 and 44 are further rendered vague and indefinite by "e.g." in the parenthetical expression "(e.g., parasitic or bacterial infections)" because it is unclear whether the limitation(s) following "e.g." are part of the claimed invention. See MPEP § 2173.05(d).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Applicant's arguments with respect to the claims have been considered but are moot in view of the new ground(s) of rejection.

Claims 1-4, 17-21, 36, and 39-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Giovanini *et al.* (Exp. Neurol., 148:523-543, 1997), taken with Galpern *et al.* (Experimental Neurology, 140:1-13, 1996).

Giovanini *et al.* teach a method of treating a mammalian xenogeneic subject having spinal cord damage by administering to the subject a composition comprising an isolated spinal cord cell obtained from a human fetus, such that treatment of spinal cord damage is obtained upon administration of the composition (see, e.g., pages 523-524, under "Materials and Methods", and page 526-527, under "Suspension transplants").

Giovanini *et al.* do not disclose that the spinal cord cell is obtained from a pig, or an embryonic pig at the claim-designated stage of differentiation. However, in view of the teachings of Galpern *et al.* of the lack of availability of human fetal tissue, the difficulties in storing human fetal tissue, and that a means for circumventing the limitations associated with human fetal neural transplantation by grafting fetal neuroblasts derived from a xenogeneic donor, such as a pig, which allows for the sterile harvesting of large quantities of pathogen-free tissue of the desired embryonic age, and the prior art teachings of using porcine neurons to reconstruct neuronal circuitries *in vivo* (see, e.g., pages 1 and 2, under "Introduction"), it would have been obvious for one of skill in the art to modify the method of Giovanini *et al.* by substituting the human fetal spinal cord cells for pig spinal cord cells at the desired embryonic age to overcome the limitations associated with obtaining human fetal tissue for transplantation as taught by Galpern *et al.*

It would have been obvious for one of ordinary skill in the art at the time the claimed invention was made to obtain a composition of pig embryonic spinal cord cells at the appropriate stage of differentiation for the purpose of using the cells in a method of treating a mammalian xenogeneic subject suffering from spinal cord damage comprising administering the pig embryonic spinal cord cells to the subject. One of ordinary skill in the art would have been motivated to use pig as a source of cells for transplantation, for the reasons taught by Galpern *et al.* as set forth above. Moreover, one of skill in the art would have had a high expectation of successfully obtaining and using the cells in a method of treating spinal cord damage in view of the teachings of Giovanini *et al.* that administration of spinal cord cells to a xenogeneic mammal results in the claim-designated effect, i.e., treatment of spinal cord damage.

Thus the claimed invention as a whole was clearly *prima facie* obvious at the time the claimed invention was made especially in the absence of sufficient, clear, and convincing evidence to the contrary.

Claims 1, 8, 10-12, 15, 16, 18, 25, 26, 28-31, 33, and 34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Giovanini *et al.* (Exp. Neurol., 148:523-543, 1997), taken with Galpern *et al.* (Experimental Neurology, 140:1-13, 1996), as applied to claims 1-4, 17-21, 36, and 39-44 above, and further in view of Chappel (WO 95/26741, 1995).

Giovanini *et al.* teach a method of treating a mammalian xenogeneic subject having spinal cord damage by administering to the subject a composition comprising an isolated spinal cord cell obtained from a human fetus, such that treatment of spinal cord damage is obtained upon administration of the composition (see, e.g., pages 523-524, under "Materials and Methods", and page 526-527, under "Suspension transplants").

Giovanini *et al.* do not disclose that the spinal cord cell is obtained from a pig, or an embryonic pig at the claim-designated stage of differentiation. However, in view of the teachings of Galpern *et al.* of the lack of availability of human fetal tissue, the difficulties in storing human fetal tissue, and that a means for circumventing the limitations associated with human fetal neural transplantation by grafting fetal neuroblasts derived from a xenogeneic donor such as a pig which allows for the sterile harvesting of large quantities of pathogen-free tissue of the desired embryonic age, and the prior art teachings of using porcine neurons to reconstruct neuronal circuitries *in vivo* (see, e.g., pages 1 and 2, under "Introduction"), it would have been obvious for one of skill in the art to modify the method of Giovanini *et al.* by substituting the human fetal spinal cord cells for pig spinal cord cells at the desired embryonic age to overcome the limitations associated with obtaining human fetal tissue for transplantation as taught by Galpern *et al.*

The above references do not teach altering at least one MHC class I antigen on the spinal cord cell surface to inhibit rejection of the cell when introduced into the subject, wherein the alteration comprises contacting the cell prior to introduction into the subject with at least one

anti-MHC class I antibody or fragment thereof, which binds to the MHC class I antigen on the cell surface but does not activate complement or induce lysis of the cell, or wherein the anti-MHC class I antibody is an anti-MHC class I F(ab')2 fragment, and wherein the anti-MHC class I F(ab')2 fragment is a F(ab')2 fragment of a monoclonal antibody PT85. In addition, the above references do not teach administering an anti-inflammatory agent, wherein the anti-inflammatory agent is a steroid such as methylprednisolone. However, Chappel (WO 95/26741, 1995) teaches altering MHC class I antigens on cells suitable for transplantation by using a combination of molecules, W6/32 and PT85 monoclonal antibodies, such as F(ab')2 fragments, to alter two different epitopes on the same human MHC class I antigen (see page 2, lines 27-31). This alteration reduces the immunogenicity of a cell suitable for transplantation into a xenogeneic recipient in which two or more epitopes of an antigen on the cell surface which stimulates an immune response against the cell in the recipient are altered. The cells and methods of the invention can greatly improve the effectiveness of allogeneic or xenogeneic graft transplantation, with fewer side effects than immunosuppressive drugs such as cyclosporin (see page 2, lines 32-37). A preferred method for altering the epitopes on an antigen on a donor cell is by contacting the cell with the two different molecules (see, e.g., page 5, lines 31-38). The preferred antibody fragment for altering an epitope is a F(ab')2 fragment. The Fc portion of the antibody is removed thereby generating a F(ab')2 fragment, thereby providing an antibody which binds the epitopes to be altered such that they are unable to fix complement, thus preventing donor cell lysis (see, e.g., page 6, lines 3-26). The method can be applied to any type of cell which is suitable for transplantation (see, e.g., page 11, lines 37-39). A preferred non-human cell is a porcine cell, and preferred cell types include neural cells, for transplantation into a subject (see, e.g., page 12, lines 1-11). Chappel also teach using immunosuppressive drugs in conjunction with a steroid such as methylprednisolone to further reduce rejection of transplanted cells (see, e.g., page 16, lines 29-37).

It would have been obvious for one of ordinary skill in the art at the time the claimed invention was made to obtain a composition of pig embryonic spinal cord cells at the appropriate

stage of differentiation for the purpose of using the cells in a method of treating a mammalian xenogeneic subject suffering from spinal cord damage comprising administering the pig embryonic spinal cord cells to the subject. One of ordinary skill in the art would have been motivated to use pig as a source of cells for transplantation, for the reasons taught by Galpern *et al.* Moreover, one of ordinary skill in the art would have had a high expectation of successfully obtaining and using the cells in a method of treating spinal cord damage in view of the teachings of Giovanini *et al.* that administration of spinal cord cells to a xenogeneic mammal results in the claim-designated effect, i.e., treatment of spinal cord damage. In addition, it would have further been obvious to mask the spinal cord cell with the anti-MHC class I F(ab')2 fragment of a monoclonal antibody, PT85, and to further provide a steroid such as methylprednisolone in the composition for administration in view of the teachings of Chappel that masking of the cell and providing methylprednisolone are means for reducing rejection of transplanted cells.

Thus the claimed invention as a whole was clearly *prima facie* obvious at the time the claimed invention was made especially in the absence of sufficient, clear, and convincing evidence to the contrary.

Claims 1, 5-7, 13, 14, 18, 22-24, 31, 32, 35, 37, and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Giovanini *et al.* (Exp. Neurol., 148:523-543, 1997), taken with Galpern *et al.* (Experimental Neurology, 140:1-13, 1996), as applied to claims 1-4, 17-21, 36, and 39-44 above, and further in view of Fraser (WO 96/14398, 1996), Rosenbluth *et al.* (Experimental Neurology, 147:172-182, 1997), and Wang *et al.* (Neuroscience, 65:973-981, 1995).

Giovanini *et al.* teach a method of treating a mammalian xenogeneic subject having spinal cord damage by administering to the subject a composition comprising an isolated spinal cord cell obtained from a human fetus, such that treatment of spinal cord damage is obtained upon administration of the composition (see, e.g., pages 523-524, under "Materials and Methods", and page 526-527, under "Suspension transplants").

Giovanini *et al.* do not disclose that the spinal cord cell is obtained from a pig, or an embryonic pig at the claim-designated stage of differentiation. However, in view of the teachings of Galpern *et al.* of the lack of availability of human fetal tissue, the difficulties in storing human fetal tissue, and that a means for circumventing the limitations associated with human fetal neural transplantation by grafting fetal neuroblasts derived from a xenogeneic donor, such as a pig, which allows for the sterile harvesting of large quantities of pathogen-free tissue of the desired embryonic age, and the prior art teachings of using porcine neurons to reconstruct neuronal circuitries *in vivo* (see, e.g., pages 1 and 2, under "Introduction"), it would have been obvious for one of skill in the art to modify the method of Giovanini *et al.* by substituting the human fetal spinal cord cells for pig spinal cord cells at the desired embryonic age to overcome the limitations associated with obtaining human fetal tissue for transplantation as taught by Galpern *et al.*

The above references do not teach a composition comprising spinal cord cells and a neurotrophic factor, wherein the neurotrophic factor is selected from brain-derived neurotrophic factor, platelet-derived neurotrophic factor, neural growth factor, ciliary neurotrophic factor, neurotrophin-3, neurotrophin 4/5 and basic fibroblast growth factor. However, Fraser *et al.* teach isolation of porcine neural cells, which by definition, includes both nerve cells, i.e., neurons, and their precursors and glial cells, e.g., oligodendrocytes and astrocytes, and their precursors (see, e.g., page 10, lines 7-11). The neural cells can be obtained from any location in the pig central nervous system (see, e.g., page 10, line 28-29). It is well known in the art that the spinal cord is part of the central nervous system. Although Fraser *et al.* do not specifically teach administering oligodendrocytes or astrocytes to damaged spinal cord areas, Rosenbluth *et al.* teach treating spinal cord injured xenogeneic mammalian subjects comprising administering oligodendrocytes (see, e.g., page 173, under "Materials and Methods", and page 173-176, under "Results") and Wang *et al.* teach treating spinal cord injured xenogeneic mammalian subjects comprising administering astrocytes (see, e.g., page 974, left column, and page 976-979, under "Results"). Thus, it would have been obvious to administer oligodendrocytes or astrocytes to spinal cord injured xenogeneic mammalian subjects in a method of treating spinal cord injury.

It should be noted that Fraser *et al.* also teach that to promote the survival of the porcine cells in the recipient subject, growth factors, such as brain-derived neurotrophic factor, ciliary neurotrophic factor, neurotrophin-3, neurotrophin 4/5, basic fibroblast growth factor, and nerve growth factor can be included in the cell composition for transplantation (see, e.g., page 35, line 12, through page 36, line 26). Thus, inclusion of neurotrophic factors to the composition for administration to a mammalian xenogeneic subject would have been obvious to one of ordinary skill in the art to promote the survival of porcine cells in recipient subjects. In addition, Fraser *et al.* teach isolation of neural cells from a pig predetermined to be free from at least one organism selected from the group consisting of zoonotic, cross-placental and neurotropic organisms (see, e.g, page 19, lines 30-36). From the teachings of Fraser *et al.*, it would have been obvious to select spinal cord cells which are free from potential pathogenic organisms as well as to provide in a composition for administration to a subject appropriate growth factors which promote the survival of the cells in the xenogeneic mammalian subject in a method of treating spinal cord damage. Moreover, it would have been obvious to treat humans, such as those suffering from amyotrophic lateral sclerosis in view of the teachings of Fraser et al that such a degenerative disease can be treated by administering porcine cells (see, e.g., page 6, lines 26-35).

It would have been obvious for one of ordinary skill in the art at the time the claimed invention was made to obtain a composition of pig embryonic spinal cord cells, such as neurons, as disclosed by Fraser *et al.*, or oligodendrocytes, as disclosed by Rosenbluth *et al.*, or astrocytes, as disclosed by Wang *et al.*, at the appropriate stage of differentiation for the purpose of using the cells in a method of treating a mammalian xenogeneic subject suffering from spinal cord damage comprising administering the pig embryonic spinal cord cells to the subject. One of ordinary skill in the art would have been motivated to use pig as a source of cells for transplantation, for the reasons taught by Galpern *et al.* Moreover, one of ordinary skill in the art would have had a high expectation of successfully obtaining and using the cells in a method of treating spinal cord damage in view of the teachings of Giovanini *et al.* that administration of spinal cord cells to a xenogeneic mammal results in the claim-designated effect, i.e., treatment of spinal cord damage.

In addition, it would have further been obvious to provide a composition comprising pathogen-free spinal cord cells for administration to a xenogeneic subject in need thereof in view of the teachings of Fraser *et al.*, and Galpern *et al.*, of the availability and suitability of obtaining such pathogen-free cells. Furthermore, including the appropriate claim-designated growth factors in the cell composition for administration to a subject would have been obvious and well within the purview of one of ordinary skill in the art in view of the teachings of Fraser *et al.* that inclusion of growth factors enhances the survival of the administered cells in the subject.

Thus the claimed invention as a whole was clearly *prima facie* obvious at the time the claimed invention was made especially in the absence of sufficient, clear, and convincing evidence to the contrary.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet M. Kerr whose telephone number is (703) 305-4055. Should the examiner be unavailable, inquiries should be directed to John LeGuyader, Supervisory Primary Examiner of Art Unit 1633, at (703) 308-0447. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 305-7401. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist whose telephone number is (703) 308-0196.

Janet M. Kerr, Ph.D.
Patent Examiner
Group 1600

JOHN L. LeGUYADER
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600